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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,461	04/17/2001	Robert Leroy Heinrikson	6309.N CP	8815

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,461	HEINRIKSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,23-32 and 34-48* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 35-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-32,34,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-21-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20, 23-32, 34-48 are currently pending and are present for examination. Claims 23-32, 34, 47-48 are now under consideration. Claims 1-20, 35-46 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 4-6-03, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn the previous rejections under 35 U.S.C. 112, 2nd paragraph in view of claim amendment and argument. The rejection of claims under 35 U.S.C. 102(e) has also been withdrawn in view of the affidavit filed under Rule 1.132.

The Declaration filed under 37 CFR 1.132 filed 9-8-03 is sufficient to overcome the rejection of claims 23, 26-27, 33, 45-46 under 35 U.S.C. 102(e) as being anticipated by Fiscella et al. (Accession No. AAU07424, 12-18-01 and WO 01/79253, Oct, 2001, filed on 4-11-01 with an effective US filing date 4-18-00, published in English with US as a designated State, Jumbo Document, 308 pages) based upon the showing by Ms Julie Lyons that the invention entitled "Full length cloning and characterization of a heparanase II, a novel human heparanase paralog" was shown to her and filed in the Pharmacia and Upjohn Co. prior to April 18, 2000.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23 (c-f), 26-29, 34, 47(c-f)-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide with SEQ ID NO:2 or amino acids 42-534 of SEQ I D NO:2 having a heparanase enzyme activity, does not reasonably provide enablement for polypeptides or compositions comprising amino acids 42 through 129 or 42 through 161 or 130 through 534 or 162 through 534 of SEQ ID NO:2 encoded by polynucleotide comprising nucleotides 148-411, 148-507, 412-1626 of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 23 (c-f), 26-29, 34, 47(c-f)-48 are so broad as to encompass any or all polypeptides comprising amino acids 42 through 129 or 42 through 161 or 130 through 534 or 162 through 534 of SEQ ID NO:2 including variants, mutants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the making and using of fragments broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's

sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The disclosure is limited to teaching the nucleotide and encoded amino acid sequence SEQ ID NO:2 or amino acids 42-534 as having heparanase activity. It would require undue experimentation by the skilled artisan to use the claimed polypeptides with an undefined function/activity. The specification is limited to teaching the making and use of SEQ ID NO: 2 or amino acids 42-534 of SEQ ID NO:2 as a heparanase but provides no guidance with regard to the making of variants, fragments or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for a large number of variants, mutants or fragments, as encompassed by the instant claims, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of specific polypeptide fragments of SEQ ID NO:2 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting heparanase activity; (B) the general tolerance of heparanase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying amino acid residues in SEQ ID NO:2 with an expectation of obtaining the desired biological function; (E) specific activities associated with fragments claimed and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including fragments of SEQ ID NO:2 without showing that such fragments have activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of fragments of SEQ ID NO:2 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous rejection under 35 U.S.C. 112, Ist paragraph, for lack of enablement, applicants argue that Examiner's rejection does not comply with the law to the extent that it requires that the disclosed fragments must have enzymatic activity to be patentable and that the law merely requires that the fragments have a patentably utility and that the specification provide guidance on how to make and use the invention without undue

experimentation. Examiner agrees with the above argument by the applicant regarding the law that "it merely requires that the disclosed fragments have patentable utility" and that is the reason why this rejection is in place. While it is clear that SEQ ID NO:2 has heparanase activity and can be used for such a reaction, applicants have not associated any activity to the claimed fragments. Without an activity associated with the fragments those skilled in the art would not how to use it and therefore, Examiner maintains that claims are not enabled.

Next, applicant argues that the specification teaches that the fragments are result of intracellular processing of full length SEQ ID NO:2 and the fragments have the utility as size markers to establish the processing of full length protein. However, using fragments of a protein as a size markers is not a specific utility by itself and any polypeptide fragments can be used as size markers. Unless fragments are associated with a novel and specific activity Examiner maintains the above rejection.

Claims 23(c-f), 26-29, 34, 47(c-f) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23, 26-29, 34, 47 are directed to polypeptide fragments. Claims 23, 26-29, 34, 47 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides that have not been described in the claims. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the characterization

of the structure has been provided by applicants which would indicate that they had possession of the claimed genus of polypeptides. The claims do not contain any disclosure of the function of all the polypeptide sequences encompassed, including fragments within the scope of the claimed genus. The genus of polypeptides claimed is a variable genus including peptides which may have different functions. Therefore functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection in the previous Office action, applicant improperly concludes that "Examiner apparently takes the position that any claim which recites the transitional term "comprising" lacks written description and demands that if the Examiner continues to hold this view the authority to support that position be made of record. However, such a conclusion is in error. Examiner makes the following of record that he has based all the rejections in this Office action and every other Office action on the M.P.E.P and Guidelines provided by the Office. Examiner has maintained the above rejection because of lack of function for the claimed polypeptide fragments. Applicant argues that "Patent Office has identified no other structural characteristics that are necessary to identify the genus". It appears that applicant

is confused with the rejection. Actually the rejection states that said polypeptides lack function and Examiner has not questioned the structure at all.

Applicant refers to example 14 of the Written Description Guidelines and argues that the situation is identical in the instant case and that in the example the genus is defined by a 95% identity limitation with the disclosure of a single species. Examiner agrees that in example 14 of the Guidelines such a situation exists. However, the instant claims are not in identical situation. It should be noted that said claim in the example satisfies the written description by providing both the structure (i.e., 95% sequence identity) and the function (i.e., catalyzes the reaction of A→B) which is what lacking in the instant claims.

Applicant also states that the if Examiner maintains the rejection, then he should clarify what function is deemed critical. In response Examiner asserts that the heparanase activity is the critical function (if said fragments have heparanase activity) and that his assertion is based on the main invention of the applicant.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 31 is directed to an isolated heparanase II consisting essentially of an isolated "human heparanase polypeptide" comprising the amino acid sequence from residue 42 through 161 and residue 162 through 534 of SEQ ID NO:2.

The examiner maintains the position that the single representative disclosed species, i.e., SEQ ID NO:2, fails to represent the entire genus of claimed human heparanase polypeptides (underline added for emphasis).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic materials, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a single human polypeptide is described as SEQ ID NO:2 having heparanase activity. This description also adequately describes a genus, within the sequence identity limitation of the instant claims, of polypeptides having this particular function. Those sequences that are "human" are a subset of this genus of polypeptides having SEQ ID NO:2 and having heparanase activity. The specification fails to define those structural features of SEQ ID NO:2 that are commonly possessed by members of the genus that distinguish them from other "non-human" polypeptides. Thus, one skilled in the art cannot visualize or recognize the

identity of the members of the genus. As such, this single representative species does not adequately describe this subset according to its structure so that one of skill in the art can visualize and distinguish those amino acid sequences that are human, particularly in view of the larger genus that includes both human and non-human sequences. Therefore, the instant claims are not adequately described.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-32, 34, 47-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Freeman et al. (Biochem. J. 1998, Vol. 330:1341-1350). This rejection is based upon the public availability of a printed publication. Claims 23-32, 34, 47-48 of the instant application are drawn to polypeptide with SEQ ID NO:2 having human platelet heparanase activity and polypeptides comprising fragments of the same, which applicants call as heparanase-II and a composition comprising the same. Freeman et al. disclose a human heparanase enzyme purified from platelet and demonstrate that the purified enzyme is 1700 fold pure and provide a composition comprising the same. The reference does not provide the amino acid sequence of the enzyme. However, Examiner takes the position that the amino acid sequence of any enzyme (a polypeptide) is an inherent characteristic and therefore as the enzyme in the reference has the same activity and the same source as described by the applicants (i.e., human platelets, see page

35, 2nd paragraph of the specification), the enzyme in the reference (isolated from human platelets) and the enzyme claimed by the applicants are one and the same. Therefore, Freeman et al. anticipate claims 23-32, 34, 47-48 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

In response to the previous Office action, applicant has traversed the above rejection. Applicant reminds the Examiner of the standard set forth in *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991), according to which

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter **is necessarily present in the thing described in the reference** and that it would be so recognized by persons of ordinary skill. *In re Oelrich*, 212 USPQ 323, 326 (C.C.P.A. 198 1) (quoting *Hansgirg v. Kemmer*, 40 USPQ 665, 667 (C.C.P.A. 193%) provides: Inherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. (Emphasis added)
>
> And
>
> *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (B.P.A.I. 1990)
>
> [T]he examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

Applicant argues that Examiner has not met the burden required as above and provides no basis in fact or technical reasoning other than simply stating that he "takes the position" that Freeman et al. anticipates the invention and that Freeman simply discloses heparanase activity and a molecular weight. Examiner respectfully disagrees that he has not met the standard set forth in *Continental Can Co. USA v. Monsanto Co.*, or that of *Ex parte Levy* as well as with applicant's argument that Examiner has not provided any technical reasoning and that Freeman et al. has simply disclosed heparanase activity and a molecular weight.

This is because as per the standard set forth by *Continental Can Co. USA v. Monsanto Co.*, the amino acid sequence **is necessarily present in the thing described in the reference** and that it would be so recognized by persons of ordinary skill. It is fundamental knowledge that polypeptides are made up of amino acid sequences. Any basic biochemistry book can provide evidence for the same. It is also well recognized by all those practicing the art that polypeptides and specifically enzymes are made up of amino acids. If applicants have any evidence against the above reasoning, Examiner requests them to make it of record. Next, as per *Ex parte Levy,* Examiner has indeed provided technical reasoning to support inherency, i.e., that the reference enzyme and the enzyme of the invention is from the same source. Applicants have isolated the heparanase from human platelets (see page 35, "*Identification and full-length cloning of a heparanase paralog*---Molecular definition of **human platelet heparanase** II was achieved using a combination of protein sequencing .....) and the enzyme in the reference is also isolated from human platelets. While applicants have indeed compared two heparanase sequences, the prior art heparanase is identical to the heparanase claimed in the instant claims. Applicants' argument that Examiner has not provided any technical reasoning or showing of fact is highly

misplaced. In contrast, applicant's argument that Freeman et al. simply disclose heparanase and a molecular weight and therefore does not anticipate has absolutely no scientific reasoning. For all the above reasons, the above rejection is maintained.

Conclusion

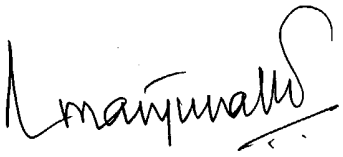
None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura

Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

August 3, 2004